DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857



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NOV 25 2008

Re: Docket No. FDA-2008-P-0329

Dear Dr. Aikman:

This responds to your citizen petition dated May 30, 2008 (Petition) and supplements to the Petition dated July 18, 2008 (First Osmotica Supplement), September 11, 2008 (Second Osmotica Supplement), September 26, 2008 (Third Osmotica Supplement), and October 9, 2008 (Fourth Osmotica Supplement) regarding venlafaxine hydrochloride (HCl) extended-release tablets. Your Petition requests that the Food and Drug Administration (FDA or the Agency) refrain from approving any pending abbreviated new drug application (ANDA) for venlafaxine HCl extended-release tablets that cites Effexor XR (venlafaxine HCl) extended-release capsules (NDA 20-699) as the reference listed drug (RLD) and was submitted based upon an approved petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(2)(C)) (suitability petition) for the change in dosage form. You request that FDA require any pending applicant seeking approval for venlafaxine HCl extended-release tablets to cite Osmotica Pharmaceutical's (Osmotica) approved venlafaxine HCl extended-release tablets (NDA 22-104) as the RLD and, in accordance with section 505(j)(2)(D)(i) of the Act, submit a new ANDA for the product. You further request that "FDA require any such ANDA applicant to conduct new bioequivalence studies comparing its proposed drug product to Osmotica's approved drug product" (Petition at 1 to 2).

We have carefully reviewed your Petition, your Supplements, and the six comments on your Petition submitted to the public docket by Winston & Strawn LLP on behalf of Sun Pharmaceuticals Industries, Ltd., and affiliates (Sun) on June 13, 2008 (First Sun Comment), June 20, 2008 (Second Sun Comment),[1] July 2, 2008 (Third Sun Comment), August 20, 2008

[1] The comments submitted by Winston & Strawn LLP on behalf of Sun on June 13, 2008, and June 20, 2008, did not contain the verification required by section 505(q)(1)(I) of the Act, notwithstanding their arguments for applying section 505(q)(1)(A) of the Act to Osmotica's Petition (see section II.F of this Response). Without the required verification, FDA would have been unable to "accept for review any supplemental information or comments on a petition" that relates to approval of a pending application submitted under section 505(b)(2) or 505(j) of the Act (505(q)(1)(I) of the Act). Although counsel for Sun subsequently provided two verifications corresponding to the comments submitted on June 13, 2008, and June 20, 2008, for inclusion in these earlier-filed comments, we note that the plain language of the Act requires that supplemental information or comments on a petition "is signed and *contains* the following verification" (505(q)(1)(I) of the Act) (emphasis added). Accordingly, a petitioner or commenter that had failed to include the required verification with its original submission would need to withdraw the original submission and resubmit the supplemental information or comment, signed and containing the required verification. Because FDA employees discussed the option of a subsequently-filed verification with Sun's counsel and agreed to accept it, we have reviewed each of Sun's comments submitted to the public docket.

FDA-2008-P-0329



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(Fourth Sun Comment), August 26, 2008 (Fifth Sun Comment), and September 26, 2008 (Sixth Sun Comment).[2] For the reasons described in further detail in this response, your Petition is granted.

## I. BACKGROUND

### A. Venlafaxine Products

On October 20, 1997, Wyeth Pharmaceuticals, Inc. (Wyeth) obtained approval for Effexor XR (venlafaxine HCl) 37.5-milligram (mg), 75-mg, 100-mg,[3] and 150-mg extended-release capsules for the treatment of major depressive disorder.[4] Effexor XR subsequently was approved for the treatment of generalized anxiety disorder in 1999, treatment of social anxiety disorder in 2003, and treatment of panic disorder in 2005.

On April 16, 2003, Lachman Consultant Services, Inc. (Lachman) submitted a suitability petition requesting permission to file an ANDA for a drug product, venlafaxine HCl extended-release tablets, 37.5 mg, 75 mg, and 150 mg, that differed from Effexor XR, the RLD, in dosage form (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).[5] FDA determined that Lachman's request for a change in dosage form (from extended-release capsules to extended-release tablets) was a type of change authorized by section 505(j)(2)(C) of the Act, and granted Lachman's suitability petition on March 30, 2005.[6] The approval of the suitability petition would permit an ANDA to be submitted for venlafaxine HCl extended-release tablets, 37.5 mg, 75 mg, and 150 mg, that referred to the corresponding strengths of Effexor XR extended-release capsules as the basis for ANDA submission (see 21 CFR 314.94(a)(3)). The letter from FDA granting Lachman's suitability petition stated, in relevant part:

> The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the FDA has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the FDA.

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[2] The verification that accompanied the Fifth Sun Comment stated, in relevant part, that "the information upon which I have based the action requested herein first become known to me between August 20 and August 25, 2008" (Fifth Sun Comment at 2). We note, however, that the Fifth Sun Comment contains data from a bioequivalence study completed earlier by Sun. In addition, the bioequivalence study data in the Fifth Sun Comment also was referenced in the Fourth Sun Comment dated August 20, 2008, thus suggesting that the information first became known to Sun's counsel prior to August 20, 2008. The certification and verification requirements of section 505(q)(1)(H)-(I) of the Act should encourage petitioners and commenters to make timely and thorough submissions, containing all relevant information and contentions that are known or should be known by the petitioner or commenter at that time. Serial submissions that do not contain newly available information are strongly discouraged.

[3] The 100-mg strength of Effexor XR (venlafaxine hydrochloride) extended-release capsules has been discontinued from marketing.

[4] Strengths of venlafaxine hydrochloride are expressed as the base equivalent throughout this response.

[5] See Docket No. 2003P-0159/CP. Docket number 2003P-0159 was changed to FDA-2003-P-0351 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[6] See FDA-2003-P-0351-0001 (March 2005 Suitability Petition Response).

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> The listed drug products to which you refer in your ANDA must be the drug products upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission. *Please note that once an application is approved for a product that is the same as the subject of an approved petition that drug product will be the listed drug. Thereafter, a petition may not be utilized as the basis for submission of an ANDA.*

(March 2005 Suitability Petition Response at 2; emphasis added.)

Prior to approval of any ANDA submitted based upon the approved suitability petition,[7] a new drug application (NDA) submitted through the approval pathway described by section 505(b)(2) of the Act (505(b)(2) application) was approved for venlafaxine HCl extended-release tablets. On May 20, 2008, Osmotica's 505(b)(2) application for 37.5-mg, 75-mg, 150-mg, and 225-mg venlafaxine HCl extended-release tablets (NDA 22-104) was approved for treatment of major depressive disorder and social anxiety disorder.[8] The approval of Osmotica's NDA 22-104 was based on the Agency's finding of safety and effectiveness for Effexor XR extended-release capsules and supported by comparative bioavailability data (see Petition at 4).

### B. Abbreviated Approval Pathways Available Under the Act for a Change in Dosage Form to a Listed Drug Product

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created sections 505(b)(2) and 505(j) of the Act. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[9] Section 505(j) of the Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the RLD[10]) with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness

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[7] It should be noted that on April 29, 2005, Wyeth submitted a petition for reconsideration of the March 30, 2005, decision on Lachman's suitability petition, and a petition to stay approval of Lachman's suitability petition pending a decision on the petition for reconsideration. As discussed in section II.A of this response, we have determined that the intervening approval of an NDA for the product described by the suitability petition precludes an ANDA applicant from referring to the suitability petition and listed drug described therein as its basis for submission. Accordingly, it is not necessary to address the issues raised by Wyeth's petition for reconsideration at this time (see discussion in section II.E of this response).

[8] Osmotica did not seek approval of venlafaxine hydrochloride extended-release tablets for the treatment of generalized anxiety disorder or panic disorder, indications for which unexpired marketing exclusivity and/or method-of-use patents are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Effexor XR, the listed drug relied upon in support of Osmotica's 505(b)(2) application.

[9] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[10] As defined at 21 CFR 314.3(b), *reference listed drug* means "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application."

for the RLD, and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the Act.

Section 505(j)(2)(C) of the Act provides that an applicant may submit a suitability petition to FDA requesting permission to file an ANDA that differs from a listed drug in route of administration, dosage form, or strength, or that has one different active ingredient in a combination drug product. A suitability petition is submitted to the public docket, and third parties may submit comments and information regarding the changes proposed in the petition (see 21 CFR 10.20, 10.30, and 314.93). In the preamble to the 1989 proposed rulemaking to implement the Hatch-Waxman Amendments, FDA invited comment on its policy of making suitability petitions available to the public, implicitly recognizing that public disclosure of a suitability petition filed by or on behalf of a prospective ANDA applicant that describes proposed changes to a listed drug could adversely affect the prospective applicant's commercial interests should another applicant obtain approval for the change first. After considering comments submitted to the public docket that supported or opposed confidentiality of suitability petitions, the Agency determined that the public availability of suitability petitions "would enhance the decisionmaking process" ("Abbreviated New Drug Application Regulations; Final Rule" (57 FR 17950 at 17952, April 28, 1992)) (1992 Final Rule). FDA maintains a Web page that lists suitability petitions filed after March 31, 1999, by drug name and petition number and provides information on the status of the petition (approved, denied, withdrawn, or pending).[11]

FDA will grant a suitability petition unless it determines that the safety and effectiveness of the proposed change from the listed drug cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA (see section 505(j)(2)(A),(C) of the Act and § 314.93(e)(1)(i)). However, a suitability petition will not be granted for a product for which a pharmaceutical equivalent has been approved, as the suitability petition process is intended for a proposed "drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug" (§ 314.93(b)). In such a case, the ANDA applicant should refer to the approved pharmaceutical equivalent designated by the Agency as the RLD as its basis for ANDA submission. We previously have explained:

> if a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the Act and 21 CFR 314.93 seeking to change to a tablet dosage form.[12]

After approval of a drug product that is a pharmaceutical equivalent to the drug described in the suitability petition, the suitability petition and listed drug described therein may no longer be used as the basis for ANDA submission by applicants with pending ANDAs or by prospective

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[11] See http://www.fda.gov/cder/ogd/suitabil.htm.

[12] See November 30, 2004, response to Donald O. Beers and William F. Cavanaugh, Jr., re: Docket No. 2004P-0386/CP1 & RC1 at 9, note 13 (Fenofibrate Citizen Petition Response). Docket number 2004P-0386 was changed to FDA-2004-P-0089 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

ANDA applicants.[13] Prospective ANDA applicants are apprised of this risk when a suitability petition is granted (see section I.A of this response). Accordingly, applicants with pending ANDAs (and prospective ANDA applicants) would be required to cite the pharmaceutically equivalent drug product as their RLD and meet other applicable statutory requirements for ANDA approval.

An applicant seeking approval for a drug product that differs from a listed drug in route of administration, dosage form, strength, or active ingredient, as described above, has the option of: (1) requesting permission, through a suitability petition, to submit an ANDA; or (2) submitting a 505(b)(2) application.[14] Submission of an application under section 505(b) would be required if investigations were necessary to evaluate the safety and effectiveness of the changed product; however, the 505(b)(2) pathway also may be used to seek approval for changes to an approved product that do not require additional investigations.[15]

Section 505(b)(2) of the Act describes an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug). A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.

Both ANDA and 505(b)(2) applicants are subject to applicable periods of marketing exclusivity granted to the listed drug relied upon and are required to submit an appropriate patent certification or statement for each patent that claims the listed drug or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the Act (see section 505(b)(2)(A)-(B) and

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[13] We note, however, that it is the Agency's practice not to rescind approval of the suitability petition under these circumstances (see discussion in section II.E of this response).

[14] In the preamble to the 1992 final rule implementing the Hatch-Waxman Amendments, we stated:

> The preamble to the proposed rule (54 FR 28872 at 28891) asked whether FDA should adopt a policy whereby a 505(b)(2) application for a drug product with a change in dosage form, strength, route of administration, or active ingredient would be treated as a petition under section 505(j)(2)(C) of the act. Most comments opposed such a policy, asserting that the policies and procedures for 505(b)(2) applications are or should be distinct from those for suitability petitions. After careful consideration, the agency believes that the policy would prolong review of 505(b)(2) applications and suitability petitions. Consequently, FDA will not adopt the proposed policy.

1992 Final Rule (57 FR 17950 at 17952).

[15] See draft guidance for industry on *Applications Covered by Section 505(b)(2)* (October 1999) (noting, with reference to the 1992 Final Rule, that "an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act") (505(b)(2) Draft Guidance).

505(j)(2)(A)(vii)-(viii) of the Act). However, only the sponsor of an application submitted under section 505(b) can, and is required to, file with FDA information on each patent claiming the drug or method of using the drug for listing in the Orange Book (see section 505(b)(1) and 505(c)(2) of the Act).

### C. Therapeutic Equivalence Ratings

The Orange Book provides FDA's therapeutic equivalence evaluations for approved multisource prescription drug products and facilitates knowledge about the availability of generic drugs that are substitutable at the pharmacy level. Drug products are classified as therapeutically equivalent if they are approved as safe and effective, pharmaceutically equivalent,[16] bioequivalent, adequately labeled, and manufactured in compliance with Current Good Manufacturing Practice regulations (see Orange Book, 28th edition, at vii). As noted in the Preface to the Orange Book, "FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product" when administered to patients under the conditions specified in the labeling (Orange Book, 28th edition, at vii).

Upon approval of an NDA or an ANDA submitted based upon an approved suitability petition for a drug product that differs from a listed drug in route of administration, dosage form, strength, or active ingredient, the new single-source[17] drug product would be designated as the RLD for any subsequent generic applicants (see discussion in section II.A of this response). FDA has explained that "[b]y designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs" (Orange Book, 28th edition, at x; see also 1992 Final Rule, 57 FR 17950 at 17954). As the new drug product would be single-source, there would be no therapeutic equivalence rating until a second pharmaceutically equivalent product was approved.

In limited circumstances, FDA may designate two or more RLDs, generally "only when there are at least two potential reference drug products which are not bioequivalent to each other" (Orange Book, 28th edition, at xv). FDA's policy on designating an additional RLD for multiple source products is set forth in the preamble to the 1992 Final Rule and also described in the preface to the Orange Book. In the 1992 Final Rule, we stated in relevant part: "FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown

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[16] As defined at 21 CFR 320.1(c):

> *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

[17] A single-source drug product is one for which "there is only one approved product available for that active ingredient, dosage form, route of administration, and strength" (Orange Book, 28th edition, at xi).

bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA" (57 FR 17950 at 17958).[18] We further explained that a company that seeks to market a "generic version of a listed drug that is not designated as the reference listed drug may petition the Agency through the Citizen Petition procedure (see 21 CFR 10.25(a) and [21] CFR 10.30)" (Orange Book, 28th edition, at x).

As further discussed in section II.A of this response, we have required applicants with pending ANDAs submitted based upon an approved suitability petition to change the basis for ANDA submission from the drug product described in the suitability petition to the newly-approved, pharmaceutically equivalent drug product designated by the Agency as the RLD and provide evidence adequate to meet the statutory requirements for ANDA approval. Prior to December 8, 2003, this change in the basis for ANDA submission and submission of any necessary data[19] in support of the change could have been accomplished by means of an amendment to the ANDA.

### D. Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)

On December 8, 2003, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173, 117 Stat. 2066) was enacted. The MMA amended section 505(j) of the Act to generally prohibit an ANDA applicant from amending an ANDA "to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted [to FDA]" (section 505(j)(2)(D)(i) of the Act). As a result, a change in the listed drug referenced as the basis for ANDA submission can be made only by the submission of an entirely new ANDA.

In the *Federal Register* of November 4, 2004 (69 FR 64314), FDA announced the availability of a draft guidance for industry, issued as required by section 505(j)(2)(D)(iii) of the Act, that defined the term "listed drug" for purposes of section 505(j)(2)(D) with respect to amendments and supplements to an ANDA (see draft guidance for industry on *Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Questions and Answers*) (Draft Guidance on Listed Drugs). In the Draft Guidance on Listed Drugs, we noted that our definition of the term "listed drug" is set forth in § 314.3, and that we did not intend to

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[18] See, e.g., April 18, 2005, response to Robert W. Pollock, Lachman Consultant Services, Inc. re: Docket No. 2004P-0504/CP1 (requesting designation of DiaBeta as a second RLD for glyburide tablets, 5 mg). Docket number 2004P-0504 was changed to FDA-2004-P-0466 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[19] In the context of a change in the basis for ANDA submission, we note that a decision whether new information relating to bioequivalence was necessary to meet the statutory standard for approval and assign a therapeutic equivalence rating (and, if so, the nature of that new information) was made on a case-by-case basis.

amend that definition to implement section 505(j)(2)(D) of the Act.[20] Although different strengths of an approved drug product continue to be regarded as different listed drugs, the Act expressly permits an applicant to amend or supplement an ANDA to seek approval of a different strength (see section 505(j)(2)(D)(ii) of the Act).

The Draft Guidance on Listed Drugs described general considerations for when a separate ANDA should be submitted for a different listed drug. The draft guidance explained:

> When the Orange Book identifies as a separate listed drug a product with the characteristics (e.g., active ingredient, dosage form, route of administration) for which the applicant is seeking approval, the applicant should submit a separate ANDA referencing the corresponding listed drug. The applicant should not submit a supplement or amendment to its pending or approved application to seek approval for such a change.

(Draft Guidance on Listed Drugs at 3.)

The *Federal Register* notice announcing the availability of the Draft Guidance on Listed Drugs noted the following:

> A situation that is not considered in this guidance is that where a pending ANDA was submitted referencing a petition approved under section 505(j)(2)(C) of the [Act]..., and another application is approved for the product described in the petition before the pending ANDA is approved. FDA has not completed its analysis of this situation, and therefore the draft guidance does not cover it.

(69 FR 64314 at 64315; November 4, 2004.)

Since 2004, the Agency has been presented with the situation described in this *Federal Register* notice (see section II.C of this response). Although the Draft Guidance on Listed Drugs does not address the implications of amendments to the Act made by the MMA for a change in RLD under these circumstances, there has been no change in the Agency's scientific requirements for a generic drug product to demonstrate bioequivalence to the pharmaceutically equivalent product designated as the RLD.

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[20] As defined at 21 CFR 314.3(b):

> *Listed drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

## II. ANALYSIS

### A. A Suitability Petition May Not Be Used as the Basis for ANDA Submission After an NDA Is Approved for the Same Drug Product Described in the Approved Suitability Petition

Osmotica states that "FDA's policy has been to require an applicant with a pending ANDA subject to an approved suitability petition to change RLD once the Agency approves another application for the same drug product [i.e., a pharmaceutical equivalent] described in the approved suitability petition" (Petition at 2).

In contrast, Sun asserts that "the purported FDA 'policy' that Osmotica is relying upon does not exist" (Third Sun Comment at 5). Instead, Sun maintains that because its submission of an ANDA[21] for venlafaxine HCl extended-release tablets based on an approved suitability petition and the listed drug described therein (Effexor XR capsules) predates the approval of a 505(b)(2) application for Osmotica's venlafaxine HCl extended-release tablets, FDA should allow Sun to obtain approval of its ANDA using a non-pharmaceutically equivalent product as its basis for ANDA submission (see First Sun Comment at 7). Sun bases this contention, in part, on its interpretation of FDA's letter approving the suitability petition and the fact that Sun's ANDA and Osmotica's 505(b)(2) application in support of approval for venlafaxine HCl extended-release tablets are described as containing a similar quantity and type of data (see First Sun Comment at 7). Sun further maintains that "[i]f FDA grants Osmotica's petition, it will seriously undercut the entire suitability petition process. No company can feel secure relying on an approved suitability petition when at any given time (unbeknownst to the ANDA applicant) another application could be approved such that they will be required to effectively start all over again" (Sixth Sun Comment at 4).

As discussed in this section, our requirement that an applicant with a pending ANDA subject to an approved suitability petition change the RLD upon FDA approval of an NDA for the same drug product described in the approved suitability petition reflects the Agency's judgment that considerations regarding an ANDA's limited reliance on an approved suitability petition are outweighed by the need for a clear determination of therapeutic equivalence for a generic drug product and protection of intellectual property rights accorded an NDA holder. We address the Agency's precedent on this issue in section II.C of this response, below.

#### 1. The March 2005 Suitability Petition Response

Sun maintains that in the March 2005 Suitability Petition Response "FDA made clear (a) that every ANDA for extended release tablets "must" use the capsules as the RLD and (b) that this

[21] FDA's regulation at 21 CFR 314.430(b) provides that "FDA will not publicly disclose the existence of an application or an abbreviated application before an approval letter is sent to the applicant under § 314.105 or tentative approval letter is sent to the applicant under § 314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged." Because the existence of a pending ANDA at issue in this Petition has been disclosed or acknowledged in the public submissions to the Petition docket, FDA may disclose the existence of the ANDA and name the applicant. In analyzing and responding to the Petition, the Agency has relied on the description of the pending ANDA provided in submissions to the docket made on behalf of its sponsor.

mandate would apply to every ANDA (unlike [sic] Sun's) *submitted* before the approval of any tablets" (First Sun Comment at 3) (emphasis in original). Sun also contends that 21 CFR 314.101(d)(3) of our regulations "states that an ANDA must refer to 'a' listed drug and, thus, contemplates and permits reference to one RLD, even if the reference to a different RLD may also be possible" (Second Sun Comment at 2).

*FDA Response:*

Sun is correct that every ANDA submitted based upon the approved suitability petition before an NDA is approved for the extended-release tablet dosage form must reference the extended-release capsule dosage form as its basis for ANDA submission. In our petition response granting permission to submit an ANDA for venlafaxine HCl extended-release tablets, we stated that "[t]he listed drug products to which you refer in your ANDA must be the drug products upon which you based this petition" (March 2005 Suitability Petition Response at 2). This statement reflects the requirement in our regulations that "[f]or an abbreviated new drug application based on an approve[]d petition under §10.30 of this chapter or §314.93, the reference listed drug must be the same as the listed drug approved in the petition" (§ 314.94(a)(3)(i)). This regulatory provision confirms, in the case of multiple RLDs for the same drug product or multiple listed drugs from which a change in route of administration, dosage form, strength, or active ingredient could be made, that an ANDA submitted in reliance upon an approved suitability petition must identify as its RLD the listed drug for which FDA made its assessment in approving the suitability petition. As described in section I.B of this response, FDA's approval of a suitability petition provides notice to other potential ANDA applicants (as well as potential NDA applicants) that FDA has found the changes described in the petition to be permitted by statute for submission of an ANDA.

However, in the letter granting a suitability petition, FDA also explains to prospective ANDA applicants the implications of any intervening approval of an application for a drug product that is the same as (i.e., a pharmaceutical equivalent to) the product described in the suitability petition with respect to any ANDAs that had not yet been submitted or approved. FDA advises applicants considering reliance on the suitability petition for submission of an ANDA: "Please note that once an application is approved for a product that is the same as the subject of an approved petition that drug product will be the listed drug. Thereafter, a petition may not be utilized as the basis of submission of an ANDA" (March 2005 Suitability Petition Response at 2). This standard statement ensures that potential applicants considering submission of an ANDA based on the suitability petition recognize the potential risks associated with this regulatory pathway.

Sun proposes to interpret this statement, incorrectly, as requiring that only ANDAs submitted to the Agency after the approval of Osmotica's venlafaxine HCl extended-release tablets could not rely on the suitability petition and Effexor XR as the basis for ANDA submission (see First Sun Comment at 3). Sun emphasizes that their ANDA had been submitted to the Agency prior to approval of Osmotica's NDA (see First Sun Comment at 7).

Sun suggests that the phrase "basis for ANDA submission" refers to the act of submitting an ANDA to FDA for filing (see First Sun Comment at 7). This interpretation, however, is

inconsistent with our long-standing practice and the use of the term "basis for ANDA submission" in our regulations to describe the RLD upon which the ANDA proposes to rely as its basis for approval. Section 314.94 (21 CFR 314.94) of our regulations describes the content and format requirements for an ANDA, including the "[b]asis for abbreviated new drug application submission." The "basis for ANDA submission" means that "[a]n abbreviated new drug application must refer to a listed drug" (§ 314.94(a)(3)). Our regulations provide that ANDAs may be submitted for "[d]rug products that are the same as a listed drug" or "[d]rug products that have been declared suitable for an abbreviated new drug application submission by FDA through the petition procedures..." (21 CFR 314.92(a)). As we explained in the suitability petition response, "once an application is approved for a product that is the same as the subject of an approved petition that drug product will be the listed drug" (March 2005 Suitability Petition Response at 2). Osmotica's 505(b)(2) application for venlafaxine HCl extended-release tablets, 37.5 mg, 75 mg, and 150 mg,[22] was approved on May 20, 2008, and is the same drug product as the drug product proposed in the suitability petition approved on March 30, 2005. Accordingly, Osmotica's drug product became the RLD and the suitability petition and the listed drug described therein (Effexor XR capsules) could no longer be cited as the basis for ANDA submission. Once a new RLD was identified, the pending ANDA could not "contain the information required by FDA with respect to the . . . dosage form . . . that is not the same as that of the reference listed drug" and the Agency will refuse to approve the ANDA (21 CFR 314.127(a)(5)) (see also 21 CFR 314.127(a)(12)). Thus, any ANDA seeking approval for venlafaxine HCl extended-release tablets is required to refer to Osmotica's NDA 22-104 as its RLD.[23]

With respect to Sun's contention that "[u]nder 21 C.F.R. § 314.101(d)(3), an ANDA may properly refer to any appropriate RLD when multiple potential RLDs are available" (Second Sun Comment at 2), Sun has not provided and we have not identified a basis for this assertion in § 314.101(d)(3) or elsewhere in our regulatory scheme for generic drug products (see also section II.F of this response).[24] Apart from the limited circumstances in which FDA may designate two or more RLDs for the same drug product (see section I.D of this response), Sun appears to propose that any ANDA applicant has the option of selecting any dosage form of an approved drug product as its RLD irrespective of whether a pharmaceutically equivalent product has been approved. As discussed in sections II.A.2-3 of this response, this approach would diminish the utility and accuracy of FDA's therapeutic equivalence determinations and

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[22] Osmotica also obtained approval for a 225-mg venlafaxine hydrochloride extended-release tablet; however, this strength was not requested in Lachman's suitability petition. We note that a separate suitability petition, filed by Kendle Regulatory Affairs on behalf of Sun, for the 225-mg and 300-mg strengths of venlafaxine hydrochloride extended-release tablets is pending (see FDA-2008-P-0247).

[23] Although Sun maintains that "[e]ven if, hypothetically, a tablet product had been listed as an RLD before Sun submitted its ANDA, Sun still could have obtained permission to list Wyeth's capsules as the RLD – a request what [sic] could have been justified by Sun's own business considerations" (Third Sun Comment at 7), this contention is plainly incorrect. As we explained in section I.B of this response, a suitability petition will not be granted for a product for which a pharmaceutical equivalent has been approved.

[24] Section 314.101(d)(3) states in relevant part: "FDA ... may not consider an [ANDA] to be received if any of the following applies: ... (3) The ... abbreviated application is incomplete because it does not on its face contain information required under ... section 505(j) ... and § 314.94."

potentially allow ANDA applicants to circumvent otherwise applicable patent and exclusivity rights accorded the NDA holder for the pharmaceutically equivalent RLD.

2. Scientific Justification for Requiring a Change in RLD for an ANDA Submitted Based Upon an Approved Suitability Petition

Sun states that there is "no scientific basis for the agency action Osmotica seeks" (First Sun Comment at 7). Sun asserts that "both Sun's and Osmotica's products are bioequivalent to Effexor XR and both rely on Effexor XR's safety and effectiveness data. Requiring an additional bioequivalency comparison between the two products would demonstrate nothing more scientifically" (First Sun Comment at 7).

Sun subsequently acknowledged, in the context of requesting that its proposed product be designated as a second RLD, that "it is possible that Sun's and Osmotica's products are *not* bioequivalent to each other even though they are both bioequivalent to Wyeth's capsules. If they are not bioequivalent — a distinct possibility considering Sun and Osmotica rely on different underlying technologies — then they are 'different products' rather than the 'same products' meeting the requirements of sameness under § 505(j)(2)(A)" (Third Sun Comment at 6; emphasis in original).

Sun later asserted that Osmotica's product is not bioequivalent to Sun's product based upon data that purports to "show[] that Sun's product is bioequivalent to Effexor XR capsules under *both* fed *and* fasted conditions. Osmotica's tablet, by contrast, is bioequivalent to Effexor XR in the fed but not the fasted state..." (Fourth Sun Comment at 1).[25]

*FDA Response*

FDA requires that a generic drug product be shown to be bioequivalent to the RLD as a condition of approval (see section 505(j)(2)(A)(iv) of the Act; see also 21 CFR 314.127(a)(6)(i)). Approval of an ANDA for venlafaxine HCl extended-release tablets would mean that FDA has determined that the product is therapeutically equivalent to or substitutable for the RLD, Osmotica's venlafaxine HCl extended-release tablets.

In an ANDA submitted based upon an approved suitability petition, an applicant is demonstrating the bioequivalence of its proposed drug product to the listed drug identified in the approved petition (which differs from the proposed drug product in route of administration, dosage form, or strength, or that has one different active ingredient in a combination drug product). However, upon approval of an NDA for the same drug product described in the approved suitability petition, we have required an applicant with a pending ANDA to change its basis for ANDA submission to the newly approved drug product to ensure that there has been a clear determination of bioequivalence to the pharmaceutically equivalent drug product so that it meets the requirements for ANDA approval.

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[25] We note that current draft guidance on *Venlafaxine Hydrochloride* regarding bioequivalence recommendations for extended-release capsules states that "due to safety concerns, bioequivalence studies under fasting conditions are not recommended." Venlafaxine hydrochloride extended-release capsules and tablets are labeled for administration with food.

If a proposed drug product with the change described in a suitability petition (e.g., a change in dosage form) is submitted in an NDA (either a "stand-alone" NDA or 505(b)(2) application), the drug product proposed in the NDA need not be bioequivalent to the previously approved drug product. For example, a 505(b)(2) applicant may develop a different dosage form of a drug product that is intentionally more bioavailable than a previously approved product.[26] Further, a 505(b)(2) applicant may have relied upon a different listed drug in support of its 505(b)(2) application than the listed drug identified in the suitability petition. Such a 505(b)(2) applicant would need to establish that its proposed reliance on FDA's finding of safety and/or effectiveness for a listed drug is scientifically appropriate (e.g., through comparative bioavailability data) and submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug (see 21 CFR 314.54). Accordingly, should an NDA be approved for a drug product that is a pharmaceutical equivalent to the drug product described in the approved suitability petition, it is appropriate from both a scientific and regulatory standpoint that the pending ANDA identify the pharmaceutically equivalent product as its new basis for ANDA submission under § 314.94(a) and meet applicable bioequivalence requirements with respect to the pharmaceutically equivalent drug product so that it may be determined to be therapeutically equivalent. Although we note that Sun has asserted that a change in its RLD to Osmotica's venlafaxine HCl extended-release tablets would require Sun to "demonstrate bioequivalence to a product that has never been the subject of any direct clinical testing [other than bioavailability studies]" (Sun comment at 5-6; see also Sun comment at 2), this approach reduces the potentially confusing proliferation of pharmaceutically equivalent drug products that have not demonstrated therapeutic equivalence, and ensures that ANDAs for venlafaxine HCl extended-release tablets will be therapeutically equivalent and thus substitutable for the RLD, Osmotica's venlafaxine HCl extended-release tablets.

3. Intellectual Property Rationale for Requiring Change in RLD for an ANDA Submitted Based Upon an Approved Suitability Petition

Sun contends that there is no legal or policy reason to require Sun to submit a new ANDA citing Osmotica's product as the RLD and containing studies to demonstrate what Sun describes as "bioequivalence to a bioequivalent product" (First Sun Comment at 2). Sun further maintains that "FDA is not legally required to mandate that Sun change its RLD and as a matter of policy it should exercise its discretion to permit Sun to rely on Effexor XR pursuant to the approved suitability petition" (Sixth Sun Comment at 2).

*FDA Response*

FDA's policy of requiring all pending ANDA applicants to change their basis for ANDA submission upon approval of an NDA for the same drug product described in the suitability petition is intended to ensure that ANDA applicants do not circumvent the patent certification requirements of section 505(j)(2)(A)(vii)-(viii) of the Act through the suitability petition

[26] Compare 21 CFR 314.54(b).

process.[27] In addition, our policy would appropriately protect any marketing exclusivity that has been granted to the newly-approved RLD.

Section 505(j)(2)(A)(vii) of the Act requires that ANDA applicants provide a certification with respect to each patent that claims the RLD or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed by the NDA holder under subsection 505(b) or 505(c) of the Act. For each patent listed in the Orange Book, the ANDA applicant must submit either a paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the ANDA applicant is seeking approval (section 505(j)(2)(A)(viii) of the Act). An applicant submitting a paragraph IV certification is required to give notice of the patent challenge to the holder of the NDA for the RLD and each owner of the patent that is the subject of the certification.[28] Submission of an ANDA for a drug product or the use of a drug product claimed in a patent is an act of patent infringement if the product described in the ANDA is intended to be marketed before patent expiration (see 35 U.S.C. 271(e)(2)).

As discussed in section I.B of this response, an NDA applicant, including an applicant for a 505(b)(2) application, is required to submit information to FDA on "any patent which claims the drug . . . or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture[,] use, or sale of the drug" (see section 505(b)(1) and 505(c)(2) of the Act). This patent information may include information on relevant patents listed in the Orange Book for the listed drug relied upon in support of the 505(b)(2) application as well as patents that claim the drug product proposed in the NDA (e.g., a drug product patent related to a change in dosage form).

Although currently there are no patents listed in the Orange Book for Osmotica's venlafaxine HCl extended-release tablets that were not already listed for Effexor XR, this may not be the case for other 505(b)(2) applications (or stand-alone 505(b)(1) applications) approved for a drug product that is a pharmaceutical equivalent to the drug product described in a suitability petition. Further, any argument that the current absence of additional patents claiming Osmotica's product should allow a pending ANDA applicant for venlafaxine HCl extended-release tablets to continue to reference Effexor XR as its basis for ANDA submission would deprive Osmotica of certain intellectual property rights should a new patent be issued prior to ANDA approval.

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[27] An ANDA submitted based upon an approved suitability petition "must include appropriate patent certification(s) and an exclusivity statement with respect to the listed drug which served as the basis for the approved suitability petition" (Orange Book, 28th edition, at xxi).

[28] Notice of a paragraph IV certification includes, among other things, "a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed" (section 505(j)(2)(B)(iii) of the Act). In addition, with respect to patents submitted prior to submission of the 505(b)(2) application or ANDA (excluding an amendment or supplement to the application), if the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there will be a statutory 30-month stay of approval of the ANDA while the patent infringement litigation is pending (section 505(j)(5)(B)(ii) of the Act).

Section 505(c)(2) of the Act provides, among other things, that if an NDA holder "could not file patent information under subsection [505(b) of the Act] because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued."

Thus, FDA's policy of requiring all pending ANDA applicants to change their basis for ANDA submission upon approval of an NDA for the same drug product described in the suitability petition rests upon a sound intellectual property justification.[29]

### B. Section 505(j)(2)(D)(i) of the Act Generally Prohibits an ANDA Applicant From Amending an ANDA to Refer to a Different RLD

Osmotica states that section 505(j)(2)(D)(i) of the Act, added by the MMA, "precludes an ANDA applicant with a pending application from changing RLD. Instead, a new application must be submitted citing the appropriate RLD" (Petition at 2). In contrast, Sun contends that the plain language of this section of the Act would lead to "absurd results" thus requiring analysis of the legislative intent of this statutory provision (Third Sun Comment at 9). Sun asserts that "[t]he relevant legislative history makes clear that, under these circumstances, § 505(j)(2)(D) does not mandate the filing of a brand new ANDA" (Third Sun Comment at 9). Rather, Sun maintains that section 505(j)(2)(D) "is designed to address situations where an ANDA applicant changes its *own product* in a way that requires the applicant to switch RLDs" (Third Sun Comment at 9) (emphasis in original).

*FDA Response*

We disagree with Sun's contention that application of the plain language of section 505(j)(2)(D)(i) of the Act, added by the MMA, would lead to "absurd results" and necessitates analysis of legislative intent (see, e.g., *United States v. Gonzales*, 520 U.S. 1, 6 (1997) ("Given the straightforward statutory command, there is no reason to resort to legislative history"). Section 505(j)(2)(D)(i) of the Act states: "An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to [FDA]." Thus, if at any time before approval of the ANDA, a different drug product is approved that is the pharmaceutical equivalent to the product

[29] Sun also asserts that "if Sun is required to file a brand new ANDA, it will lose its [180-day] exclusivity, which it earned by being the first generic to file a Paragraph IV certification as to venlafaxine hydrochloride extended-release tablets" (Third Sun Comment at 8; see also Sixth Sun Comment at 4). We note, however, that the 180-day exclusivity provisions of the Act would block approval of subsequent ANDAs for the same drug product (i.e., extended-release tablet dosage form) that also contain a paragraph IV certification to the patent listed for the same listed drug (see 21 CFR 314.107(c)). Since FDA would not approve any ANDAs (including Sun's ANDA) that did not identify the corresponding strengths of Osmotica's venlafaxine hydrochloride extended-release tablets as the RLD, there is no 180-day exclusivity to lose or subsequent ANDAs to block (see, e.g., Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule, 59 FR 50338 at 50354 (October 3, 1994) (stating that "certain changes in an ANDA (e.g., a change in the listed drug) would amount to a new filing for purposes of §314.107(c)(2)"). It should be noted that the first applicant to submit a substantially complete ANDA for venlafaxine hydrochloride extended-release tablets that identifies Osmotica's venlafaxine hydrochloride extended-release tablets as the RLD and contains a paragraph IV certification to a listed patent may be eligible for a 180-day period of marketing exclusivity during which approval of subsequent ANDAs for the same drug product that also contain a paragraph IV certification to the patent will not be granted.

in the ANDA and is designated as the RLD, the ANDA applicant may not amend their application to rely upon the new RLD. This type of change must be submitted in a new ANDA. The statutory language in section 505(j)(2)(D)(i) of the Act "emphatically covers the facts of this case" (see *United States v. Clintwood Elkhorn Mining Co.*, 128 S. Ct. 1511, 1518 (2008)(advising that "[t]he 'strong presumption' that the plain language of the statute expresses congressional intent is rebutted only in 'rare and exceptional circumstances'" (internal citations omitted)).

The MMA also amended section 505(j)(5)(B)(iii) of the Act to restrict the availability of a 30-month stay of approval in certain circumstances involving amendments and supplements to an application. Section 505(j)(5)(B)(iii) of the Act permits a 30-month stay of approval while patent infringement litigation is pending only with respect to patents for which the NDA holder submitted information to FDA prior to the date of submission of an ANDA that refers to the listed drug claimed by the patent. Amendments and supplements to an ANDA are excluded from the category of applications to which this provision applies. Accordingly, our application of the plain language of section 505(j)(2)(D)(i) of the Act is intended to ensure that an ANDA applicant does not use the amendment or supplement process to evade the possibility of a 30-month stay of approval that would have applied if an ANDA applicant sought approval for the changed product in the original application.

This approach thus ensures that ANDA applicants provide an appropriate patent certification or statement to any patents listed for the new RLD. Under Sun's interpretation of section 505(j)(2)(D)(i) of the Act, if a patent was listed for a drug product approved in an NDA and designated as the RLD, and an applicant was permitted to amend a pending ANDA that had been submitted based upon an approved suitability petition to refer to the new RLD, even a single 30-month stay would not be available should the NDA holder or patent owner initiate patent infringement litigation within the statutory time frame in response to a paragraph IV certification. Our interpretation of the MMA provisions related to the Hatch-Waxman Amendments upholds the legislative balance of facilitating the availability of generic drug products that meet the statutory requirements for approval while protecting innovator intellectual property rights (and allowing for an early resolution of any patent infringement litigation).[30]

Thus, section 505(j)(2)(D)(i) of the Act precludes Sun from amending its pending ANDA to refer to Osmotica's approved NDA for the pharmaceutically equivalent venlafaxine HCl extended-release tablets as Sun's basis for ANDA submission. Instead, Sun must withdraw its ANDA 78-978 and, if Sun wishes to pursue approval for venlafaxine HCl extended-release tablets, Sun would be required to submit a new ANDA referencing the corresponding approved strengths of Osmotica's NDA 22-104 as its RLD, submit information demonstrating that Sun's proposed product is bioequivalent to the RLD, and provide an appropriate patent certification or statement for each patent listed in the Orange Book for the corresponding strengths of NDA 22-104.

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[30] We note that our interpretation of § 505(b)(4)(A) of the Act, also added by the MMA, for 505(b)(2) applications is influenced by and intended to be consistent with section 505(j)(2)(D)(i) regarding ANDAs. Accordingly, a 505(b)(2) applicant may not amend or supplement a 505(b)(2) application to seek approval of a drug that relies on the Agency's finding of safety and/or effectiveness for a drug that is different from the drug identified in a previous submission of the application.

### C. FDA's Requirement That Sun Change Its Basis for ANDA Submission to Osmotica's Venlafaxine HCl Extended-Release Tablets Is Consistent With Agency Precedent

In support of the Petition, Osmotica cites two examples in which "FDA required a generic applicant with a pending ANDA subject to an approved suitability petition to change RLD after the Agency approved, pursuant to FDC Act § 505(b), the drug product described in the suitability petition. Importantly, in the post-MMA case, Osmotica understands that FDA required the submission of a new ANDA as a result of FDC Act § 505(j)(2)(D)(i)" (Petition at 5). Osmotica supplemented its Petition with an example in which FDA required a pending ANDA applicant to change its RLD after the Agency approved an ANDA for the oral dosage form drug product described in the suitability petition (see Second Osmotica Supplement at 4). Sun contends that the examples described in the Petition do not support the existence of FDA policy requiring an applicant to change its RLD (see Second Sun Comment at 2 to 4). Rather, Sun identifies other factors that may have necessitated the change in RLD in these cases (see Second Sun Comment at 2 to 4). Sun maintains that "FDA has approved ANDAs referencing listed drugs that differed in dosage form from the proposed generic, even when other listed drugs of the same dosage form existed" (Second Sun Comment at 5). Sun later acknowledged that "[i]n certain situations, FDA has required an applicant with a pending ANDA to change its RLD. In others it has not..." (Sixth Sun Comment at 4).

*FDA Response*

We address each of the examples provided in the Petition, the supplements to the Petition, and Sun's comments on the Petition below.

1. *Carboplatin Injection*

Osmotica cited carboplatin injection as an example of FDA's policy prior to enactment of the MMA when an NDA is approved for the same drug product described in the approved suitability petition (Petition at 5). On May 20, 1993, and November 30, 2001, FDA approved suitability petitions requesting permission to file an ANDA for carboplatin injection, 10 mg/mL, in 5 mL, 15 mL, and 45 mL vials (total drug content 50 mg, 150 mg, and 450 mg, respectively), which represented a change in dosage form (from a lyophilized powder for injection to a ready-to-use solution for injection) from the reference listed drug, Paraplatin (carboplatin) for injection, 50 mg/vial, 150 mg/vial, and 450 mg/vial (NDA 19-880).[31] On July 14, 2003, Bristol-Myers

[31] See Docket No. 1992P-0467 and 2001P-0036/PAV1. Docket number 1992P-0467 was changed to FDA-1992-P-0063 and docket number 2001P-0036 was changed to FDA-2001-P-0374 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. A second suitability petition was submitted for the same proposed change in dosage form because the first suitability petition was approved prior to implementation of the Pediatric Rule (63 FR 66632, December 2, 1998) in effect at that time. The Pediatric Rule required, among other things, an assessment of the safety and effectiveness of a new dosage form for the claimed indications in all relevant pediatric subpopulations and data to support pediatric dosing and administration (see 21 CFR 314.55). The second suitability petition requested a full waiver of the pediatric studies requirement under § 314.55(c).

Squibb Company (BMS) received approval for Paraplatin (carboplatin aqueous solution) injection (NDA 20-452), the same drug product described in the approved suitability petition.

Osmotica noted that the approval letter for ANDA 76-517, submitted on October 18, 2002, by Faulding Pharmaceutical Company, reflected the change in RLD to the newly approved NDA 20-452. ANDA 76-517 is currently held by Hospira. Sun acknowledged this carboplatin injection precedent in its first comment on the Petition, but noted that "[u]nlike here [referring to venlafaxine HCl extended-release tablets], however, the product was an injectable solution product and, thus, there was no burden in switching the RLD because no time-consuming and expensive bioequivalence studies in human volunteers were required" (First Sun Comment at 6). In its second comment on the Petition, Sun contended that "Osmotica's manufactured 'policy' was not why the FDA required Hospira to switch its RLD. Rather, Hospira's product (which did not contain mannitol) simply did not satisfy the FDA's criteria for referencing the lyophilized product (which did contain mannitol)" (Second Sun Comment at 3).

Sun's contention regarding the reason for the required change in RLD is incorrect. Subsequent to the approval of NDA 20-452, FDA notified applicants that any pending ANDAs (including tentatively approved ANDAs) that had been submitted based upon the approved suitability petition were required to change their basis for ANDA submission from NDA 19-880 to NDA 20-452 to cite the pharmaceutically equivalent RLD. In our letter to ANDA applicants, we stated the following:

> Upon approval of a product that reflects the change requested in an ANDA suitability petition, whether such an approval is pursuant to an ANDA suitability petition or an NDA, the newly approved drug product becomes a new reference listed drug (RLD). Moreover, once such a drug product is approved, the suitability petition is no longer considered a valid basis of submission for other ANDAs; all pending or new ANDA applicants must use the newly designated RLD as the "Basis of Submission." This policy helps assure that (a) the ANDA will be the same as the RLD to the extent necessary, (b) any exclusivities attached to the newly approved RLD are recognized, and (c) any patents listed for the newly approved RLD are appropriately certified to by all prospective ANDA applicants.[32]

With respect to Sun's contention regarding the difference in inactive ingredients, we note that in appropriate circumstances, FDA may grant a request for waiver under 21 CFR 314.99(b) of the requirement to use the same inactive ingredients as the RLD when an ANDA applicant is seeking approval for a parenteral formulation that is the same as a previously marketed RLD (see 21 CFR 314.99(b)).

Osmotica stated that it was "not aware of a post-MMA case in which FDA required an ANDA applicant to change RLD and submit a new application after approving a drug product under FDC Act § 505(b)(2) that is also described in an approved suitability petition" (Petition at 9). It should be noted that we required ANDA applicants that wished to pursue approval of their pending ANDA for Carboplatin Injection, 10 mg/mL, in 5 mL, 15 mL, and 45 mL vials (total

[32] See Letter dated August 12, 2004, from G. Buehler, Director, OGD, to undisclosed applicants regarding ANDAs for Carboplatin Injection, 10 mg/mL.

drug content 50 mg, 150 mg, and 450 mg, respectively) after enactment of the MMA to withdraw their pending ANDA and submit a new ANDA citing NDA 20-452 as their RLD.[33]

2. *Change from prescription to over-the-counter status*

In support of its Petition, Osmotica also cites an "analogous situation" in which applicants with pending ANDAs for a prescription drug product needed to submit new ANDAs to change the RLD (post-MMA) after the approval of a separate NDA for the RLD that switched the product from prescription to over-the-counter (OTC) status (Petition at 9 to 10). Sun maintains that Osmotica's "assert[ion] ... that the FDA requires the filing of a brand "new ANDA" whenever the RLD product is switched from prescription-only product to an over-the-counter (OTC) product ... is absolutely false" (First Sun Comment at 7). In support of its comment, Sun notes that its affiliate, Caraco Pharmaceutical Laboratories, Ltd. (Caraco) "merely was required to amend its label when Zyrtec chewable tablets (cetirizine HCl) were switched from prescription-only to OTC" (First Sun Comment at 7).

The requirement that an applicant with a pending ANDA for a prescription drug product submit a new ANDA to change its RLD after some or all conditions of use for the RLD are switched from prescription use to over-the-counter (OTC) status depends on whether the switch was approved in a separate NDA and thus resulted in a different RLD. If an NDA holder submits a supplement to their NDA seeking approval to change the drug product from prescription use to OTC status for all conditions of use (a "full switch"), the OTC product would be identified by the same NDA number and would be considered the same RLD. For example, Children's Zyrtec (cetirizine HCl) chewable tablets, 5 mg and 10 mg (NDA 21-621, Supplement 005) was approved for OTC use on November 16, 2007, through a supplement to the NDA. Accordingly, applicants with pending ANDAs were permitted to amend their applications to seek approval for cetirizine HCl chewable tablets, 5 mg and 10 mg, for OTC use and submit revised product labeling to conform with the revised labeling for the RLD as approved for OTC use. The labeling amendment submitted by Caraco (Exhibit A to the First Sun Comment) reflects this approach.

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[33] Osmotica cites a different carboplatin suitability petition as an example of FDA's policy after enactment of the MMA. On October 1, 2003, FDA approved a suitability petition requesting permission to file an ANDA for carboplatin injection, 10 mg/mL, in 60 mL vials (total drug content 600 mg), which represented a change in dosage form (from a lyophilized powder for injection to a ready-to-use solution for injection) and strength (from 450 mg to 600 mg total drug content) from the reference listed drug, Paraplatin (carboplatin) for injection, 450 mg/vial (NDA 19-880) (see Docket No. 2003P-0220/PAV1. Docket number 2003P-0220 was changed to FDA-2003-P-0123 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.) On January 9, 2004, Bristol-Myers Squibb Company (BMS) received approval for Paraplatin (carboplatin aqueous solution) injection (NDA 20-452, Supplement 001), the same drug product described in the approved suitability petition. On February 3, 2004, FDA advised the petitioner that approval of the suitability petition was suspended in light of the recent enactment of the Pediatric Research Equity Act of 2003 (PREA), which requires, among other things, that "all applications for a ... new dosage form ... contain an assessment of the safety and effectiveness of the drug for the claimed indication in relevant pediatric subpopulations unless the requirement is waived or deferred" (Letter dated Feb. 3, 2004, from G. Buehler to Faulding Pharmaceutical Company re: Docket No. 03P-0220/CP1). We note that even if the suitability petition had not been suspended, ANDA applicants would have been required to reference the approved, pharmaceutically equivalent Paraplatin as their RLD.

However, if an NDA holder sought approval for a change to OTC status for fewer than all conditions of use, a separate NDA would be required. The separate NDA would be considered a new RLD, which would necessitate that an ANDA applicant seeking approval for the OTC product identify the approved NDA for OTC use as their new RLD. After enactment of the MMA, this change in the RLD would require submission of a new ANDA.

3. *Hydrocodone Bitartrate and Acetaminophen Tablets*

Osmotica described hydrocodone bitartrate and acetaminophen tablets, a fixed-combination drug product, as an example of FDA's policy requiring a change in RLD when an application is approved for the same drug product described in the approved suitability petition (Second Osmotica Supplement at 4). On July 7, 1987, FDA approved a suitability petition requesting permission to file an ANDA for hydrocodone bitartrate and acetaminophen tablets, 10 mg/500 mg, which represented a change in strength from the RLD, Vicodin (hydrocodone bitartrate and acetaminophen) tablets, 5 mg/500 mg.[34] On June 7, 1995, Watson Laboratories, Inc. (Watson) submitted ANDA 40-148 based on the approved suitability petition for hydrocodone bitartrate and acetaminophen tablets, 10 mg/500 mg. On January 26, 1996, D.M. Graham Laboratories, Inc. received approval for ANDA 40-100 for Lortab (hydrocodone bitartrate and acetaminophen tablets), 10 mg/500 mg, based upon the same suitability petition and Lortab subsequently became the RLD for this single-source product. ANDA 40-100 is currently held by UCB, Inc. As Osmotica noted, FDA required Watson to change the RLD for its pending ANDA to the newly approved, pharmaceutically equivalent ANDA 40-100 and requested that Watson conduct dissolution testing between their 10 mg/500 mg proposed product and the new RLD to demonstrate bioequivalence (Watson's proposed change in strength continued to be eligible for a waiver of in vivo bioequivalence studies pursuant to 21 CFR 320.22(c)) (see Second Osmotica Supplement at 4, referencing FDA Review of a Waiver Request (Amendment) dated February 13, 1997, for ANDA 40-148, available at http://www.fda.gov/cder/foi/anda/97/040148ap.pdf).

4. *Reference to discontinued drug product*

Sun maintains that "FDA has approved ANDAs referencing listed drugs that differed in dosage form from the proposed generic, even when other listed drugs of the same dosage form existed" (Second Sun Comment at 5). Sun cites the following three examples in support of its contention: octreotide acetate injection; oxaliplatin injection; and selegiline HCl tablets (see Second Sun Comment at 5 and Third Sun Comment at 5 to 6).

Each of Sun's examples involves ANDAs referencing discontinued formulations of approved drug products — a different regulatory scenario than presented by an ANDA seeking approval for a change from a listed drug submitted based upon a suitability petition after an NDA has been approved for the changed product. Although Sun uses the words "suitability petition" and "citizen petition seeking a determination that the discontinued formulations ... were suitable for evaluation under an ANDA" in characterizing these examples, this inaccurately suggests that Sun's examples relate to suitability petitions submitted in accordance with § 314.93 (see Second

[34] See Docket No. 1987P-0170/PAV1. Docket number 1987P-0170 was changed to FDA-1987-P-0081 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

Sun Comment at 5). In fact, with the exception of octreotide, Sun's examples relate to citizen petitions submitted in accordance with § 314.161 (21 CFR 314.161) (relisting petitions) that request a determination regarding whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons.[35]

The examples cited by Sun do not support Sun's contention that "FDA has approved ANDAs referencing listed drugs that differed in dosage form from the proposed generic, even when other listed drugs of the same dosage form existed" (Second Sun Comment at 5). For example, the approval of octreotide acetate injection ANDAs for a duplicate of the previously approved formulation of Sandostatin (differing only in inactive ingredients) is not relevant to the issues raised in Osmotica's Petition regarding the intervening approval of an NDA for the change requested in a suitability petition. The ANDAs identified by Sun referenced a pharmaceutically equivalent product (i.e., the same dosage form) as their RLD. To the extent that another dosage form was referenced in these examples, it was only in support of a request for a waiver under 21 CFR 314.99(b) of the requirement to use the same inactive ingredients as the RLD when an ANDA applicant is seeking approval for a parenteral formulation that is the same as a previously marketed RLD.

Finally, we note that aspects of Sun's analysis reflect a basic misunderstanding of the relisting petition process. Sun incorrectly suggests that drug products listed in the discontinued section of the Orange Book are no longer listed drugs and that FDA's evaluation of an ANDA referencing a pharmaceutically equivalent discontinued product is inappropriate (see Third Sun Comment at 6).

### D. An ANDA for Venlafaxine HCl Extended-Release Tablets Must Contain Data Demonstrating That the Proposed Drug Product Is Bioequivalent to the RLD, Osmotica's NDA 22-104

Osmotica states that FDA should require any ANDA for venlafaxine HCl extended-release tablets to "conduct new bioequivalence studies comparing their proposed drug product to Osmotica's approved drug product" (Petition at 2).[36] Osmotica represented to the Agency that it

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[35] Our regulations require a prospective ANDA applicant that seeks approval for a duplicate of a listed drug that has been discontinued from marketing to "petition FDA to relist the drug product and provide information to show that the drug product was not withdrawn from sale due to safety or effectiveness reasons" (1992 Final Rule, 57 FR 17950 at 17953; see also 21 CFR 314.122 and § 314.161). Unless a prospective ANDA applicant is seeking permission to file an ANDA that differs from a previously approved, but discontinued, drug product in route of administration, dosage form, or strength, or that has one different active ingredient in a combination drug product, it would be unnecessary to submit a relisting petition and a suitability petition (see § 314.122). For reasons that are unclear, two petitions submitted by or on behalf of Sun included the following footnote: "Although the regulations [referring to 21 CFR 314.122 and 314.161] are consistent with relief sought, this citizen petition is submitted pursuant to section 505(j)(2)(C) of the Federal Food[,] Drug, and Cosmetic Act ... and 21 CFR § 314.93" (see Docket No. 2005P-0061/CP1 at 1, note 1 and 2006P-0298/CP1 at 2, note 1). Notwithstanding this statement, these petitions were not evaluated as suitability petitions. Docket number 2005P-0061 was changed to FDA-2005-P-0370 and docket number 2006P-0298 was changed to FDA-2006-P-0006 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[36] We need not address Osmotica's request for confirmation, should its Petition be denied, that upon approval of any currently pending ANDA the ANDA "would not be listed in the Orange Book with an AB rating to Osmotica's approved drug products" (Petition at 10, note 8).

"plans to launch the drug products approved under NDA #22-104 in the near future. Until such time as Osmotica's drug product is commercially available, Osmotica would be willing to make available to any generic applicant with a pending ANDA for Venlafaxine HCl Extended-Release Tablets an amount of the drug product (as it becomes available) sufficient for such applicant to conduct bioequivalence studies..." (Petition at 9, note 6). Osmotica subsequently amended its Petition to advise the Agency that its venlafaxine HCl extended-release tablets "will be introduced into market channels for commercial distribution the week of September 29, 2008. Therefore, Osmotica's product will be readily available to be used as the reference listed drug product for Venlafaxine Extended-release Tablet generics" (Third Osmotica Supplement at 1; see also Fourth Osmotica Supplement).

Sun contends that "[a]ny such requirement would senselessly require Sun to start all over with a new ANDA and new bioequivalence studies — a step that would serve no purpose whatsoever because the FDA has already determined that Sun's product is safe and effective given its bioequivalence to Wyeth's product (a product that, unlike Osmotica's product, was actually proven safe and effective through clinical trials)" (Second Sun Comment at 4). In this regard, Sun asserts that requiring Sun to demonstrate bioequivalence to Osmotica's product "would deprive Sun of the considerable benefit of marketing a product that is bioequivalent to Effexor XR..." (Sixth Sun Comment at 2).

Sun further states that "because Sun's and Osmotica's products have only been compared to Effexor XR but not to each other, it is possible that Sun's and Osmotica's products are *not* bioequivalent to each other even though they are both bioequivalent to Wyeth's capsules. If they are not bioequivalent — a distinct possibility considering Sun and Osmotica rely on different underlying technologies — then they are 'different products' rather than the 'same products' meeting the requirements of sameness under § 505(j)(2)(A)" (Third Sun Comment at 6) (emphasis in original). Accordingly, Sun proposes that FDA list Sun's proposed product as a second RLD for venlafaxine HCl extended-release tablets (Third Sun Comment at 7). Sun subsequently asserted that FDA should designate its proposed product as a second RLD "because fasted-state pharmacokinetic data shows that Sun's drug product is not bioequivalent to Osmotica's product" (Fourth Sun Comment at 2). In support of its proposal, Sun cites FDA's designation of a second RLD for glyburide tablets (see Fourth Sun Comment at 4).

Finally, Sun suggests, as an alternative to designating its proposed product as a second RLD, that FDA "should still approve Sun's ANDA without requiring Sun to change the listed drug referenced in the application or to resubmit the application ... [by] assign[ing] Sun's product a 'BC' therapeutic-equivalence code" (Fourth Sun Comment at 5). Sun maintains that a "BC" rating would be appropriate for their proposed product because "not only have head-to-head bioequivalence studies 'not been submitted,' but the available data actually demonstrates that the products are not bioequivalent" (Fourth Sun Comment at 5).

*FDA Response*

FDA requires that a generic drug product be shown to be bioequivalent to the RLD as a condition of approval (see section 505(j)(2)(A)(iv) of the Act). In the absence of an RLD for venlafaxine HCl extended-release tablets, ANDAs for this drug product were permitted to be

submitted based on the approved suitability petition and the listed drug (Effexor XR extended-release capsules) described therein. However, upon approval of Osmotica's NDA, Osmotica's venlafaxine HCl extended-release tablets became the RLD for all potential generic venlafaxine HCl extended-release tablets. Thus, we require each ANDA applicant developing a potential generic venlafaxine HCl extended-release tablet to demonstrate bioequivalence in vivo by comparing its proposed product to Osmotica's venlafaxine HCl extended-release tablets.[37]

We note that Sun's contention that requiring a demonstration of bioequivalence to Osmotica's product "would deprive Sun of the considerable benefit of marketing a product that is bioequivalent to Effexor XR..." overlooks a key point (see Sixth Sun Comment at 2). Sun's proposed product would not have been eligible for an "AB" therapeutic equivalence rating to Effexor XR because it sought approval for a different dosage form.

With respect to Sun's suggestion that FDA list Sun's proposed product as a second RLD for venlafaxine HCl extended-release tablets (Third Sun Comment at 7), we note that this would be inconsistent with FDA's practice in designating RLDs. Although ANDAs approved based upon a suitability petition or relisting petition might, upon approval, be designated as a first RLD, there would be no reason here to designate such a product as a second RLD because our statutory and regulatory scheme for generic drugs would require an ANDA applicant to demonstrate bioequivalence to the first RLD. Further, it is FDA's policy that a generic drug should not be used as the RLD as long as a drug product approved in an NDA is available. Sun's reference to FDA's designation of a second NDA drug product as an RLD for glyburide tablets, 5 mg, is inapposite (see Fourth Sun Comment at 4). FDA designated DiaBeta (glyburide) tablets, 5 mg, as a second RLD in addition to Micronase (glyburide) tablets, 5 mg, in response to the petition of a prospective ANDA applicant, so that DiaBeta (NDA 17-532) would not be shielded from direct competition by requiring an ANDA applicant to cite the other innovator drug product (NDA 17-498) as its basis for ANDA submission.[38] This basis for designation of a second RLD is not relevant to an ANDA product for which a pharmaceutically equivalent product was approved in an NDA and is being marketed. Sun's contentions regarding anticipated market share (see Fourth Sun Comment at 4) are simply irrelevant in this context. Sun's other examples (Adalat CC and Procardia XL (nifedipine extended-release tablets), MS Contin and Oramorph SR (morphine sulfate extended-release tablets) and Isoptin SR and Covera HS (verapamil

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[37] This required change to refer to the RLD designated by the Agency reflects FDA's longstanding policy, as explained in the preamble to its 1989 proposed rule implementing the Hatch-Waxman Amendments:

> Currently, the agency uses one product as a reference standard against which the bioequivalence of the applicant's product is compared. The agency intends to continue that practice. Usually that reference product is the innovator's product, which would also usually be the listed drug referred to by the applicant. However, if the listed drug chosen by the applicant is different from that chosen by the agency as the standard for bioequivalence determinations, the agency will require the applicant to amend its application to refer to the agency's bioequivalence reference standard as its listed drug. This policy is intended to assure that all generic products remain equivalent to a common standard and thus to each other.

Abbreviated New Drug Application Regulations; Proposed Rule (54 FR 28872 at 28882, July 10, 1989).

[38] See Docket No. 2004P-0504/PAV1. Docket number 2004P-0504 was changed to FDA-2004-P-0466 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

hydrochloride extended-release tablets)) involve drug products approved in NDAs, rather than ANDAs, and are equally unavailing (see Fourth Sun Comment at 5).[39]

Finally, Sun contends, in the alternative, that FDA should approve Sun's ANDA without requiring a change in RLD and assign a "BC" therapeutic equivalence code. This proposal is inconsistent with the statutory scheme for approval of generic drug products, which requires the submission of information showing bioequivalence to the RLD. A "B" therapeutic equivalence rating is used for "[d]rug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products" and a "BC" therapeutic equivalence rating is used for extended-release dosage forms (see Orange Book, 28th ed., at xiii and xviii). Two of the examples cited by Sun, Covera HS (verapamil) tablets and Oramorph SR (morphine) tablets, involve BC-rated drug products approved in NDAs submitted under section 505(b) of the Act, for which there is no statutory requirement for a demonstration of bioequivalence to another drug product (see Fourth Sun Comment at 6). In contrast, an ANDA for a proposed product that would be "B" rated to the RLD is not eligible for approval. The circumstances surrounding the BC-rating for ANDAs submitted by Inwood Labs for theophylline extended-release capsules and by UCB Inc for Theo-24 (theophylline) extended-release capsules are complex and not relevant to Sun's proposed product. Theo-24 was approved in 1983, prior to enactment of the Hatch-Waxman Amendments that created sections 505(b)(2) and 505(j) of the Act. Inwood Labs' theophylline extended-release capsules was approved based upon a subsequently discontinued ANDA that itself had been submitted based upon a finding of efficacy in a Drug Efficacy Study Implementation (DESI) Federal Register notice.

### E. The March 2005 Suitability Petition Response Need Not Be Rescinded Although It Is No Longer a Valid Basis for ANDA Submission

Osmotica states that "rescission of the suitability petition is appropriate in this case pursuant to 21 C.F.R. § 314.93(f) because there is new information (i.e., FDA's approval of NDA #22-104) indicating that approval should be withdrawn" (Petition at 3, note 1). Osmotica subsequently acknowledges that "[a]lthough § 314.93(f) references § 314.93(e) and none of the specific criteria in that regulation presumably apply in this case, the petition that served as the basis for Sun's ANDA submission no longer satisfies the legal requirements for approval, because there is now an NDA-approved drug product that is the RLD that is the same as the subject of the approved petition" (Supplement at 3). Sun asserts that 'there is no statutory or regulatory basis to withdraw approval of the suitability petition' (Third Sun Comment at 3).

*FDA Response*

Our regulations at 21 CFR 314.93(f) expressly confirm FDA's authority to withdraw approval of a suitability petition "if the agency receives any information demonstrating that the petition no longer satisfies the conditions under [§ 314.93(e)]" (see also 1992 Final Rule, 57 FR 17950 at

[39] See also May 17, 2000, response to Diane Servello, Andrx Pharmaceuticals, Inc. re: Docket No. 2000P-0219/CP1 ("FDA will designate a second reference listed drug when two innovator products [i.e., approved in an NDA] are bioinequivalent to each other, as is this case with Covera-HS and Isoptin SR"). Docket number 2000P-0219 was changed to FDA-2000-P-0911 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

17958). However, we need not withdraw approval of the suitability petition to implement our long-standing practice that the intervening approval of an NDA for the product described by the suitability petition precludes an ANDA applicant from referring to the suitability petition and listed drug described therein as its basis for ANDA submission. Any pending ANDA that referred to the suitability petition and the listed drug described therein would not be eligible for approval, and any newly submitted ANDA that sought to reference the suitability petition instead of the RLD identified in the Orange Book would not be received by the Agency.

### F. This Petition Has Not Delayed Approval of a Pending ANDA as Described in Section 505(q)(1)(A) of the Act

Sun maintains that "Osmotica's petition does not argue that delaying Sun's approval would protect 'public health' in any way. That alone mandates immediate denial under 21 U.S.C. §355(q)(1)(A), which states that the FDA 'shall not delay approval of a pending' ANDA absent a finding that 'a delay is necessary to protect the public health'" (First Sun Comment at 2).

*FDA Response*

Sun misconstrues the applicability of section 505(q)(1)(A) of the Act to the petition filed by Osmotica. Section 505(q)(1)(A) states that FDA "shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section because of any request to take any form of action relating to the application, either before or during consideration of the request, unless * * * (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health." Osmotica's petition did not result in a delay of approval of Sun's pending ANDA 78-978, because the intervening approval of Osmotica's NDA on May 20, 2008, rendered Sun's pending ANDA ineligible for approval — a circumstance unaffected by the filing of Osmotica's petition.[40]

This analysis with respect to section 505(q)(1)(A) of the Act is not altered by Sun's contention that "FDA would have approved Sun's ANDA but for Osmotica's citizen's [sic] petition.... The FDA even granted Sun's Pre-Launch Activities Importation Request at the end of May — *after* Osmotica obtained approval of its NDA" (Third Sun Comment at 4; emphasis in original). Sun indicates that it prepared to launch its proposed venlafaxine HCl extended-release tablet immediately upon its anticipated approval on June 13, 2008, the date on which pediatric exclusivity that had attached to U.S. Patent No. 4,535,186 (listed in the Orange Book for Effexor XR) expired (see Third Sun Comment at 4).

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[40] Indeed, any delay in conveying to Sun that their pending ANDA was ineligible for approval may be attributed to the need to address Sun's multiple, and increasingly voluminous, comments on the Petition. Further, although the ineligibility of Sun's pending ANDA was not affected by Osmotica's petition, we note that Sun contends that "[n]othing stopped Osmotica to file this petition earlier, at least upon learning that its NDA approval was imminent many weeks ago" (First Sun Comment at 4 to 5). However, the issues raised by Osmotica's petition would not have been ripe for review until approval of the 505(b)(2) application for the product that is the same as the change described in the suitability petition. Approval of an application does not take place until the issuance of an approval letter. Although certain activities by the review division may suggest that a favorable determination on an application may be forthcoming, applicants that act upon such indications necessarily do so at their own risk.

We note that section 505(a) of the Act prohibits the introduction or delivery for introduction into interstate commerce of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." FDA, however, may exercise enforcement discretion to permit certain interstate shipments of unapproved products. All manufacturers of products must recognize that all distribution activities prior to FDA approval are subject to ultimate approval of the drug products and that any FDA exercise of enforcement discretion is not a guarantee of NDA or ANDA approval. FDA has not approved an NDA or ANDA until an approval letter is sent to the applicant.

## III. CONCLUSION

We have determined that an ANDA for venlafaxine HCl extended-release tablets submitted based upon an approved suitability petition that was pending at the time of approval of Osmotica's NDA 22-104 and that seeks approval for a pharmaceutically equivalent drug product must be withdrawn, as the ANDA is required to reference the corresponding approved strengths of Osmotica's venlafaxine HCl extended-release tablets as its RLD, and section 505(j)(2)(D)(i) of the Act precludes such a change from being submitted as an amendment to an ANDA. If Sun or any other applicant wishes to pursue approval of an ANDA for venlafaxine HCl extended-release tablets, it must submit a new ANDA containing data and information required by section 505(j) of the Act for approval (including, but not limited to, a demonstration of bioequivalence to the RLD, Osmotica's venlafaxine HCl extended-release tablets).

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research